Development of Pulmonary Hypertension in patients with End Stage Renal Disease

DISSERTATION SUBMITTED IN FULFILLMENT OF THE REGULATIONS FOR THE AWARD OF M.D. GENERAL MEDICINE

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CERTIFICATE

This is to certify that the thesis entitled ***"DEVELOPMENT OF PULMONARY HYPERTENSION IN END STAGE RENAL DISEASE"*** is a bonafide work of ***Dr. PRANAV KUMAR K.V*****,** done under my direct guidance and supervision in the department of General Medicine, PSG Institute of Medical Sciences and Research, Coimbatore in fulfillment of the regulations of TamilnaduDr.MGR Medical University for the award of MD degree in General medicine.

Dr. K.Jayachandran, MD ***Principal***

Professor and HoD,

Department of Medicine,

PSG Hospitals.

DECLARATION

I hereby declare that this dissertation entitled *"**DEVELOPMENT OF PULMONARY HYPERTENSION IN END STAGE RENAL DISEASE**"* was prepared by me under the direct guidance and supervision of Professor ***Dr. K. Jayachandran, MD,*** PSG Institute of Medical Sciences and Research, Coimbatore.

The dissertation is submitted to the Tamilnadu Dr. MGR Medical University in fulfillment of the university regulations for the award of MD Degree in General Medicine. This dissertation has not been submitted for the award of any Degree or Diploma.

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INTRODUCTION

INTRODUCTION

Cardiovascular disease is the leading cause of morbidity and mortality in dialysis patients, accounting for 50%of deaths[1]. Pulmonary hypertension (PHT) comprises a group of clinical and pathophysiological entities with similar featuresbut a variety of underlying causes. There are several etiologies for PHT. Pulmonary hypertension (PHT) can be the result of heart, lung or systemic disorders. Regardlessof the etiology, morbidity and mortality from long-standingPHT exceed that expected from the causative condition [2].

PHT was frequently found in patients with chronic renal failure (CRF).Review of literature showed that in one study, PHT was found in 40% of patients with end stage renal disease (ESRD) onchronic hemodialysis therapy via arteriovenous access[5, 6]. Adekunle et al. [7] stated that PHT is an independent predictor of mortality in ESRD patients.

PHT involvesvasoconstriction and obliteration of the lumen ofsmall vessels in the lungs by plexiform lesions resultingin increased resistance to flow [2]. Proposed mechanisms for the formation of the plexiform lesion includedysregulation of endothelial growth and angiogenicresponse to local

triggers[3]. Hormonal and metabolic derangement associated with ESRD might lead to pulmonary arterialvasoconstriction and an increase of the pulmonaryvascular resistance[4].

Pulmonary artery pressure (PAP) may be further increasedby high cardiac output resulting from the arteriovenousaccess itself and also worsened by commonly occurring anemia and fluid overload [8]. Subclinical left ventriculardysfunction also occurs in patients with ESRD, and isevidenced as abnormal myocardial diastolic rather thansystolic dysfunction [9].

Local vascular tone and function of pulmonary vesselsare regulated by the balance between vasodilators, such as nitric oxide, and vasoconstrictors, such as thromboxane[10]. Patients with CRF show an endothelial dysfunctionrelated to defective nitric oxide activity, which is notcorrected by hemodialysis (HD) [11].Increased brain natriuretic hormone is associated withage, left ventricular hypertrophy, renal failure, and PHT.N-terminal pro-brain natriuretic peptide (NT-proBNP)is a byproduct of brain natriuretic peptide (BNP) that hasbeen shown to be of prognostic value in PHT[15].

AIM

AIM

In this study, we aim to find the prevalence of PHT in patients with ESRD and compare the incidence of PHT between those on hemodialysis and those on conservative management. We also compare the biochemical data of the patients with and without PHT to find out any possible associations.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

INTRODUCTION

Pulmonary hypertension (PHT) is characterized by elevated pulmonary arterial pressure and secondary right ventricular failure. It is a life-threatening condition with a poor prognosis if untreated.

DEFINITION

The definition of PHT is based upon right heart catheterization measurements. PHT is defined as a mean pulmonary artery pressure greater than 25 mmHg at rest [13]. A mean pulmonary artery pressure of 8 to 20 mmHg at rest is considered normal, while a mean pulmonary artery pressure of 21 to 24 mmHg at rest has uncertain clinical implications.

Two definitions that were previously accepted are no longer used. They include a mean pulmonary artery pressure greater than 30 mmHg with exercise (measured by right heart catheterization) [14] and a systolic pulmonary artery pressure greater than 40 mmHg (measured by Doppler echocardiography) [15]. The latter corresponds to a tricuspid regurgitant velocity of 3.0 to 3.5 m/sec.

CLASSIFICATION

Like its definition, the classification of PHT has changed. PHT was previously classified as either idiopathic pulmonary arterial hypertension (IPAH, formerly called primary pulmonary hypertension) or secondary PHT. However, it became clear that some forms of secondary PHT closely resemble IPAH in their histopathological features, natural history, and response to treatment. In an attempt to organize PHT on a mechanistic basis, the World Health Organization (WHO) classified PHT into five groups [16].

Updated clinical classification of pulmonary hypertension (Dana Point, 2008)

1. Pulmonary arterial hypertension (PAH)
    - 1.1. Idiopathic PAH
    - 1.2. Heritable
        - 1.2.1. BMPR2
        - 1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
        - 1.2.3. Unknown
    - 1.3. Drug- and toxin-induced
    - 1.4. Associated with
        - 1.4.1. Connective tissue diseases
        - 1.4.2. HIV infection
        - 1.4.3. Portal hypertension
        - 1.4.4. Congenital heart diseases
        - 1.4.5. Schistosomiasis

1.4.6. Chronic hemolytic anemia

1.5 Persistent pulmonary hypertension of the newborn

1′. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

2. Pulmonary hypertension owing to left heart disease

2.1. Systolic dysfunction

2.2. Diastolic dysfunction

2.3. Valvular disease

3. Pulmonary hypertension owing to lung diseases and/or hypoxia

3.1. Chronic obstructive pulmonary disease

3.2. Interstitial lung disease

3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern

3.4. Sleep-disordered breathing

3.5. Alveolar hypoventilation disorders

3.6. Chronic exposure to high altitude

3.7. Developmental abnormalities

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms

5.1. Hematologic disorders: myeloproliferative disorders, splenectomy

5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis

5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders

5.4. Others: tumoral obstruction, fibrosingmediastinitis, chronic renal failure on dialysis

ALK1: activin receptor-like kinase type 1; BMPR2: bone morphogenetic protein receptor type 2; HIV: human immunodeficiency virus.

Group 1 PAH—“Pulmonary arterial hypertension (PAH)".

This group consists of sporadic IPAH, heritable IPAH, and PAH due to diseases that localize to small pulmonary muscular arterioles. These include connective tissue diseases, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, chronic hemolytic anemia, persistent pulmonary hypertension of the newborn, pulmonary veno-occlusive disease, and pulmonary capillary hemangiomatosis[16].

Drug- and toxin-induced PAH is also considered group 1 PAH. Exposures to the following drugs are considered definite risk factors for PAH: aminorex, fenfluramine, dexfenfluramine, and toxic rapeseed oil [16]. In contrast, drugs that are considered likely or possible risk factors for PAH include amphetamines, L-tryptophan, methamphetamines, cocaine, phenylpropanolamine, St. John's Wort, chemotherapeutic agents, and selective serotonin reuptake inhibitors.

The hemodynamic parameters that characterize PAH include the following [16]:

•Mean pulmonary artery pressure (mPAP) >25 mmHg at rest

•Pulmonary capillary wedge pressure (PCWP) <15 mmHg

Supportive data include an increased pulmonary vascular resistance and transpulmonary gradient. The transpulmonary gradient is defined as the difference between the mean pulmonary artery pressure and the mean pulmonary capillary wedge pressure.

Group 2 PH — "Pulmonary hypertension owing to left heart disease."

PH due to systolic dysfunction, diastolic dysfunction, or valvular heart disease is included in this group [16].

Group 3 PH — "Pulmonary hypertension owing to lung diseases or hypoxemia."

This group includes PHT due to chronic obstructive pulmonary disease, interstitial lung disease, other pulmonary diseases with a mixed restrictive and obstructive pattern, sleep-disordered breathing, alveolar hypoventilation disorders, and other causes of hypoxemia [16].

Group 4 PH — "Chronic thromboembolic pulmonary hypertension."

This group includes patients with PHt due to thromboembolic occlusion of the proximal or distal pulmonary vasculature [16].

Group 5 PH — "Pulmonary hypertension with unclear multifactorial mechanisms."

These patients have PHT caused by hematologic disorders (eg, myeloproliferative disorders), systemic disorders (eg, sarcoidosis), metabolic disorders (eg, glycogen storage disease), or miscellaneous causes [16].

In the discussion that follows, PAH is used exclusively to discuss group 1, whereas PH is used to discuss groups 2 through 5. In addition, PHt is used when referring to all groups collectively.

EPIDEMIOLOGY

The prevalence of group 1 PAH in the general population is estimated to be 15 cases per one million adults [17]. Similar estimates have not been performed for the five groups of PHT collectively. The prevalence of PHT appears to vary widely among specific populations of patients:

- Systemic sclerosis (SSc, formerly called scleroderma) — An observational study of 794 patients with systemic sclerosis reported PAH in 12 percent of patients [18]. (See "Pulmonary vascular disease in systemic sclerosis (scleroderma): Definition, classification, risk factors, screening, and prognosis".)

- Portal hypertension — An observational study of 507 patients with portal hypertension reported PAH (ie, portopulmonary hypertension) in 2 percent of patients [19], while a more recent study reported PAH in about 6 percent [20]. Prevalence increases as the severity of the underlying cause of the portal hypertension (usually liver disease) worsens. (See "Portopulmonary hypertension".)
- Congenital heart disease — Congenital heart disease occurs in 8 out of every 1000 live births. Approximately 30 percent of children who do not have their congenital heart disease repaired will develop PAH [21]. (See "Evaluation and prognosis of Eisenmenger syndrome", section on 'Evaluation for congenital heart disease related pulmonary arterial hypertension'.)
- Obstructive sleep apnea (OSA) — A review of eight studies estimated that the prevalence of mild PH is 15 to 20 percent among patients with OSA [22]. (See "Cardiovascular effects of obstructive sleep apnea".)

The only national surveillance data available was collected from patients with all groups of PH from 1980 to 2002 [23]. It is unclear how changes in disease recognition, reporting, and treatment during this period impacted the results of this study.

The death rate increased from 5.2 to 5.4 per 100,000 population. The increase was greatest in African-Americans (4.6 to 7.3 per 100,000 population) and women (3.3 to 5.5 per 100,000 population). The death rate decreased in men (8.2 to 5.4 per 100,000 population) and remained stable in Caucasians (5.3 per 100,000 population). The most common cause of death was chronic lower respiratory disease from 1980 until 1999. Thereafter, PHT itself was the most common cause of death.

The hospitalization rate increased more than two-fold (40.8 to 90.1 per 100,000 population). The most common cause of hospitalization from 1980 until 1994 was chronic lower respiratory disease. Heart failure was the most common cause of hospitalization after 1994.

ETIOLOGIES

There are numerous causes of PAH including IPAH (both sporadic and hereditary), drugs and toxins, connective tissue diseases, HIV infection, portal hypertension, and congenital heart disease. Similarly, there exist many causes of PH including left heart disease, chronic obstructive pulmonary disease (COPD), interstitial lung disease, sleep related breathing disorders (eg, obstructive sleep apnea), and chronic thromboembolic pulmonary hypertension. A discussion of each follows.

Pulmonary arterial hypertension (PAH) — The following are causes of group 1 PAH.

- *Idiopathic pulmonary arterial hypertension (IPAH)* — IPAH exists when an underlying cause of the PAH cannot be identified. It is usually sporadic, with only 6 to 10 percent of patients having hereditary disease in most series.

  Abnormal bone morphogenetic protein receptor type II (BMPR2) appears to play an important role in the pathogenesis of IPAH. In sporadic IPAH, up to 25 percent of patients have abnormal BMPR2 structure or function [24-26]. In hereditary IPAH, the gene that encodes BMPR2 (IPAH1) appears to be transmitted as an autosomal dominant trait with incomplete penetrance [19,27-31]. In one study of 19 patients with hereditary IPAH, mutations likely to disrupt function of BMPR2 were found in nine patients [30]. Abnormal pulmonary vascular responses to exercise have been documented in asymptomatic carriers of IPAH1 [32].

  Hereditary IPAH may be underdiagnosed. In one study, five apparently unrelated families (almost 400 individuals) were linked by

pedigree analysis to a pair of common ancestors [33]. Among these families, 18 individuals were found to have hereditary IPAH, determined by the identification of identical BMP receptor type II mutations. Twelve of these subjects had been initially classified as having sporadic IPAH.

- *Drugs and toxins* — Appetite suppressants (eg, fenfluramine, dexfenfluramine, and diethylpropion) increase the risk of developing PAH [24,34-37]. In a case control study that compared 95 patients with PAH to 335 control patients, appetite suppressants increased the risk of PAH (odds ratio 6.3, 95% CI 3.0-13.2) [24]. The risk was particularly high when the appetite suppressants were used in the preceding year or for more than three months.

  Appetite suppressant use reported by patients with all types of PHT is greater than that reported by the general population, suggesting that appetite suppressants may initiate PHT in patients with underlying conditions that are associated with PHT, or that obesity is associated with PHT[25].

Chronic use of cocaine or amphetamines, either inhaled or intravenous, has also been associated with PAH [28,34,38,39]. In one study, cocaine or amphetamine use increased the risk of developing PAH approximately three times [34]. PAH has also been associated with recreational use of the designer amphetamine analog, 4-methyl-aminorex (ie, ice, euphoria, U-4-E-uh) [40], as well as methamphetamines, toxic rapeseed oil, and benfluorex[41].

- *Connective tissue disease* — Systemic sclerosis (SSc, also called scleroderma) causes PAH by obliteration of alveolar capillaries and narrowing of small arteries and arterioles due to pulmonary vascular disease and interstitial fibrosis. Isolated PAH appears to be more common in patients with limited SSc compared to patients with diffuse cutaneous SSc[42]. Rheumatoid arthritis and systemic lupus erythematosus (SLE) can also lead to fibrous obliteration of the pulmonary vascular bed. There is a marked female predominance and a frequent association with the Raynaud phenomenon in patients with SLE who develop PAH [26].

- *Human immunodeficiency virus (HIV)* — PAH is a rare complication of HIV infection, occurring in approximately 1 out of every 200 HIV-infected patients (0.5 percent) [43-45]. This is 6- to 12-times greater

than the prevalence of PAH in individuals without HIV infection. The cause of HIV-related PAH is uncertain, but viral and host factors both likely play an important role. HIV-related PAH is discussed in detail separately.

- *Portal hypertension* — PAH associated with portal hypertension is referred to as portopulmonary hypertension. It is discussed in detail elsewhere.

- *Congenital heart disease* — PAH due to congenital heart disease is due to pulmonary blood volume overload due to intracardiac shunting. Left to right shunts are most common, especially due to large (nonrestrictive) ventricular septal defects (VSD). PAH also occurs in patients with atrial septal defects (ASD). Noninvasive imaging — including transthoracic echocardiography, transesophageal echocardiography (TEE), and magnetic resonance imaging (MRI) — can be used to characterize cardiac anatomy and function in patients with congenital heart defects.

Pulmonary hypertension (PH) — The following are causes of group 2, group 3, group 4, or group 5 PHT.

- *Left heart disease* — Left atrial hypertension (ie, an elevated pulmonary capillary wedge pressure) requires an increased pulmonary artery systolic pressure to maintain an adequate driving force across the pulmonary vasculature. The degree of PHT that results from any given level of left atrial hypertension varies greatly from individual to individual. This reflects the multiple impediments to normal pulmonary vascular flow that can exist, including reactive vasoconstriction, vascular remodeling, and left atrial hypertension.

  Causes of left atrial hypertension include left ventricular systolic or diastolic dysfunction, mitral and aortic valve disease, restrictive cardiomyopathy, constrictive pericarditis, and left atrial myxoma.

  Heart failure and dilated cardiomyopathy are common causes of PHT. As an example, in a study of 108 patients with dilated cardiomyopathy, 26 percent had a pulmonary artery systolic pressure above 40 mmHg, as determined by echocardiography [46]. The PHT was associated with a greater likelihood of death or hospitalizations (89 versus 32 percent). Multiple factors contribute to cardiomyopathy-associated PHT including chronic pulmonary venous congestion,

recurrent transient hypoxemia, and sleep-disordered breathing [47].

The importance of mitral regurgitation as a cause of PHT was shown in a study of 41 patients with isolated severe mitral regurgitation [48]. PHT was identified in 76 percent of patients, of which 17 percent had a pulmonary artery systolic pressure greater than 70 mmHg.

- *Chronic Obstructive Pulmonary Disease (COPD)* — PHT is a common complication of COPD with a significant impact on outcome [49-51]. As an example, one study reported a five-year survival rate less than 10 percent among patients with COPD and a mean pulmonary arterial pressure greater than 45 mmHg, compared to a five-year survival rate greater than 90 percent among patients with COPD and a pulmonary arterial pressure less than 25 mmHg [51]. The prevalence of PH in patients with COPD is more strongly associated with hypoxemia than symptoms or abnormal lung function [51].

- *Interstitial lung disease (ILD)* — ILD-related PHT can exist when ILD is mild, but it is more common when hypoxemia and severe pulmonary dysfunction exist. ILD-related PH is reviewed separately.

- *Sleep related breathing disorders* — Obstructive sleep apnea (OSA) is the sleep related breathing disorder that is most often associated with PHT. Untreated OSA alone is associated with mild PHT. However, it may be associated with significant PHT when combined with obesity hypoventilation syndrome (severe obesity, diminished central respiratory drive, and daytime hypoxemia) or other causes of hypoxemia. These patients have a significant risk of mortality due to progressive PHT, corpulmonale, or arrhythmias, although the magnitude of the risk is uncertain [52,56].

- *Chronic thromboembolic disease* — Chronic proximal PE may cause severe PH in a small number of patients. The emboli are often asymptomatic and the resting arterial oxygen level may be normal; however, virtually all patients demonstrate oxyhemoglobin desaturation with exercise [54,55].

  Pulmonary angiography is unnecessary if a ventilation-perfusion (V/Q) scan is normal because a normal V/Q scan accurately excludes thromboembolic disease [56]. When thromboembolic disease exists, however, pulmonary angiography is necessary to define the extent of disease because perfusion scans tend to underestimate the extent of proximal embolization [57].

CLINICAL MANIFESTATIONS

In this section, the symptoms and signs of PHT are described. These findings may be difficult to elucidate in patients with PHT that is caused by an underlying condition, because manifestations of the underlying disease frequently obscure those of the PHT.

History

Most patients with PHT initially experience exertional dyspnea, lethargy, and fatigue, which are due to an inability to increase cardiac output with exercise [58,59]. As the PHT progresses and right ventricular failure develops, exertional chest pain (ie, angina), exertional syncope, and peripheral edema may develop. In most circumstances, angina is due to subendocardialhypoperfusion caused by increased right ventricular wall stress and myocardial oxygen demand. However, angina is occasionally caused by dynamic compression of the left main coronary artery by an enlarged pulmonary artery; this risk is greatest for patients with a pulmonary artery trunk at least 40 mm in diameter [60-62].

Passive hepatic congestion may cause anorexia and abdominal pain in the right upper quadrant. Less common symptoms of PHT include cough, hemoptysis, and hoarseness (ie, Ortner's syndrome) due to

compression of the left recurrent laryngeal nerve by a dilated main pulmonary artery.

Physical examination

The initial physical finding of PHT is usually increased intensity of the pulmonic component of the second heart sound, which may even become palpable. The second heart sound is narrowly split or single in patients with PHT and preserved right ventricular function. Splitting of the second heart sound widens as the right ventricle fails or if right bundle branch block develops.

Auscultation of the heart may also reveal a systolic ejection murmur and, in more severe disease, a diastolic pulmonic regurgitation murmur. The right-sided murmurs and gallops are augmented with inspiration.

Right ventricular hypertrophy is characterized by a prominent A wave in the jugular venous pulse, associated with a right-sided fourth heart sound, and either a left parasternal heave or a downward subxiphoid thrust.

Right ventricular failure results in systemic venous hypertension. This can lead to a variety of findings such as elevated jugular venous pressure, a right ventricular third heart sound, and a high-pitched tricuspid regurgitant murmur accompanied by a prominent V wave in the jugular venous pulse if

tricuspid regurgitation is present. In addition, hepatomegaly, a pulsatile liver, peripheral edema, ascites, and pleural effusion may exist [63,64].

Some patients with PHT due to severe COPD develop edema even in the absence of right heart failure [67]. The pathogenesis of edema in such patients is not well understood [66,67]. It has been hypothesized that edema may develop in these patients due to hypercapnia or hypoxemia. Hypercapnia is associated with an appropriate increase in proximal bicarbonate reabsorption, which minimizes the fall in arterial pH. This increase in proximal bicarbonate transport also promotes the passive reabsorption of sodium chloride and water, and may contribute to edema formation [68].

DIAGNOSTIC EVALUATION

Chest radiograph

The classic chest radiograph shows enlargement of the central pulmonary arteries with attenuation of the peripheral vessels, resulting in oligemic lung fields. Right ventricular enlargement (diminished retrosternal space) and right atrial dilatation (prominent right heart border) may also be seen. Occasionally, the underlying cause of the PHT is apparent on the chest radiograph (eg, interstitial lung disease).

Electrocardiography

The electrocardiogram (ECG) may demonstrate signs of right ventricular hypertrophy or strain, including right axis deviation, an R wave/S wave ratio greater than one in lead V1, incomplete or complete right bundle branch block, or increased P wave amplitude in lead II (P pulmonale) due to right atrial enlargement . Most ECG signs are specific but not sensitive for the detection of right ventricular disease. ECG changes cannot determine disease severity or prognosis [82,83].

Echocardiography

Echocardiography is performed to estimate the pulmonary artery systolic pressure and to assess right ventricular size, thickness, and function. In addition, echocardiography can evaluate right atrial size, left ventricular systolic and diastolic function, and valve function, while detecting pericardial effusions and intracardiac shunts [84,85].

Echocardiography uses Doppler ultrasound to estimate the pulmonary artery systolic pressure. This technique takes advantage of the tricuspid regurgitation that usually exists. The maximum tricuspid regurgitant jet velocity is recorded and the pulmonary artery systolic pressure (PASP) is then calculated:

$$PASP = (4 \times TRV \text{ squared}) + RAP$$

where TRV is the maximum tricuspid regurgitant jet velocity and RAP is the right atrial pressure estimated from the size and respiratory variation of flow in the inferior vena cava. Doppler echocardiography is limited when an adequate tricuspid regurgitant jet cannot be identified.

Patients with PHT may have echocardiographic signs of right ventricular pressure overload, including paradoxical bulging of the septum into the left ventricle during systole and hypertrophy of the right ventricular free wall and trabeculae. As the right ventricle fails, there is dilation and hypokinesis, septal flattening, right atrial dilation, and tricuspid regurgitation. The tricuspid regurgitation is not due to an intrinsic abnormality of the tricuspid valve; it is a secondary manifestation of dilation of the tricuspid annulus and right ventricle [86]. Other findings associated with pulmonary hypertension are pulmonic insufficiency and midsystolicclosure of the pulmonic valve [87]. The echocardiographic findings of PHT are summarized in the figure.

Based upon a Doppler echocardiographic study, it can be determined if PHT is likely, unlikely, or possible [88]:

- PHT is likely if the PASP is >50 and the TRV is >3.4

- PHT is unlikely if the PASP is ≤36, the TRV is ≤2.8, and there are no other suggestive findings
- PHT is possible with other combinations of findings

Doppler echocardiography may be misleading in the assessment of patients with suspected pulmonary hypertension, especially when an inadequate tricuspid regurgitant jet is over-interpreted. This was illustrated by an observational study of 65 patients with various types of PHT[89]. The pulmonary arterial pressure estimated by Doppler echocardiography was at least 10 mmHg higher or lower than that obtained by right heart catheterization in 48 percent of patients and, in many cases, the difference in pulmonary artery pressure determined by the two modalities was significantly greater than 10 mmHg. Overestimation and underestimation of pulmonary arterial pressure occurred with similar frequency, although the magnitude of the underestimation was greater. A major limitation of the study was that catheterization and Doppler echocardiography were not performed simultaneously.

The study supports our opinion that there should be a low threshold to evaluate patients with suspected pulmonary hypertension via right heart catheterization. Despite its limitations, Doppler echocardiography detects

PHT with greater accuracy than clinical history and physical examination [90,91].

Pulmonary function tests

Pulmonary function tests (PFTs) are performed to identify and characterize underlying lung disease that may be contributing to PHT. An obstructive pattern is suggestive of COPD, while restrictive disease suggests interstitial lung disease, neuromuscular weakness, or chest wall disease.

It is usually severe interstitial lung disease (with lung volumes below 50 percent of predicted) or obstructive lung disease that produces PHT. In most circumstances, PHT should not be attributed to lung disease if the PFTs are only mildly abnormal since PH itself can cause PFT abnormalities. As an example, a study of 79 patients with idiopathic pulmonary arterial hypertension (IPAH) demonstrated that more than half of patients had a mild to moderate decrease of forced expiratory volume in one second (FEV1) or forced vital capacity (FVC) compared to age and sex matched controls [92]. The diffusing capacity for carbon monoxide (DLCO) is usually decreased in PHT[92,93].

Overnight oximetry

Nocturnal oxyhemoglobin desaturation can be identified by overnight oximetry. It is common in patients with PHT and may prompt supplemental oxygen therapy during sleep [94]. Overnight oximetry is not an acceptable diagnostic test for sleep related breathing disorders, such as obstructive sleep apnea.

Polysomnography

Polysomnography is the gold standard diagnostic test for sleep related breathing disorders, such as obstructive sleep apnea (OSA). It should be performed when the clinical suspicion for OSA is high, or the results of overnight oximetry are discordant with clinical expectation.

V/Q scan

Ventilation-perfusion (V/Q) scanning is used to evaluate patients for thromboembolic disease. A normal V/Q scan accurately excludes chronic thromboembolic disease with a sensitivity of 96 to 97 percent and a specificity of 90 to 95 percent [95]. When the V/Q scan suggests that chronic thromboembolic disease exists, pulmonary angiography is necessary to confirm the positive V/Q scan and to define the extent of disease. V/Q

scans are an important part of the diagnostic evaluation because PHT due to chronic thromboembolic disease is potentially reversible with surgery.

Laboratory tests

Blood tests performed in the diagnostic evaluation of PHT include:

- HIV serology to screen for HIV-associated PHT
- Liver function tests to screen for portopulmonary hypertension
- Antinuclear antibody (ANA), rheumatoid factor (RF), and antineutrophil cytoplasmic antibody (ANCA) titers to screen for PHT due to the connective tissue diseases

In the appropriate clinical setting, laboratory studies looking for evidence of chronic hemolytic anemia (eg, sickle cell disease) or schistosomiasis are appropriate.

N-terminal pro-brain natriuretic peptide (NT-proBNP) is the precursor of brain natriuretic peptide (BNP). Both peptides are released from the myocardial tissue of the right and left ventricle when stretched. Increasing evidence suggests that NT-proBNP and BNP are helpful in diagnosing heart failure. It has been hypothesized that measurement of either peptide may also be helpful in the diagnosis of PHT, since right heart failure often

complicates PHT. Preliminary data are promising, although accuracy diminishes if renal dysfunction exists [96-99]. NT-proBNP and BNP should not be used in the routine diagnostic evaluation of patients with suspected PHT until their value is confirmed in larger prospective studies.

Exercise testing

Exercise testing is most commonly performed using the six-minute walk test (6MWT) or cardiopulmonary exercise testing. The latter can be performed with gas exchange measurements, echocardiography, and/or right heart catheterization. Exercise testing during the diagnostic evaluation of PH serves several purposes:

- Screens for alternative causes of the patient's symptoms.
- Detects exercised-induced PHT, which may be an intermediate stage that exists between normal and resting PHT[100].
- Determines the patient's World Health Organization (WHO) functional class [101], which guides therapy.
- Establishes a baseline from which the response to therapy can be measured.

- Provides prognostic information, since a longer distance walked during the 6MWT is associated with longer survival [101].

Right heart catheterization

Right heart catheterization is necessary to confirm the diagnosis of PHT and accurately determine the severity of the hemodynamic derangements. PHT is confirmed if the mean pulmonary artery pressure is greater than 25 mmHg at rest [101].

Right heart catheterization is also helpful in distinguishing patients who have group 2 PHT (PHT due to left heart disease, such as systolic dysfunction, diastolic dysfunction, or valvular heart disease) [81]. Such patients have a mean pulmonary capillary wedge pressure (PCWP) ≥15 mmHg, as measured by right heart catheterization. However, the mean PCWP alone is insufficient to definitively diagnose group 2 PHT because it may be falsely elevated due to dilatation of the pulmonary arteries and incomplete "wedging" of the balloon catheter. To avoid this dilemma, patients with a mean PCWP ≥15 mmHg should have their left heart filling pressure directly assessed by measuring the left ventricular end diastolic pressure (LVEDP) via left heart catheterization. Failure to do so means that

some patients may be incorrectly diagnosed as having group 2 PHT, which has important therapeutic implications.

The risk of incorrectly diagnosing patients with group 2 PHT on the basis of a falsely elevated mean PCWP was demonstrated by a retrospective analysis of hemodynamic data from 3926 patients with PHT who underwent simultaneous right and left heart catheterization [102]. Among the 3346 patients who had a mean PCWP >15 mmHg, 152 patients (5 percent) had a normal left ventricular filling pressure, defined as a LVEDP ≤15 mmHg. The authors of the study focused on how frequently the mean PCWP was ≤15 mmHg when the LVEDP was >15 mmHg, but it should be emphasized that the mean PCWP is virtually always less than the LVEDP because the latter reflects the pressure at the end of left atrial contraction.

An additional benefit of right heart catheterization is that the presence and/or severity of a congenital or acquired left-to-right shunt can be confirmed when noninvasive studies are not definitive.

NATURAL HISTORY

The natural history of untreated IPAH is the most extensively studied and the focus of this section. The natural history of other types of PHT is

variable and depends on the severity of both the PHT and the underlying disease.

Symptomatic patients with IPAH who do not receive treatment have a median survival of approximately three years. Symptomatic patients with PAH that is associated with another disease (eg, liver disease, systemic sclerosis [also called scleroderma]) generally have a worse prognosis than patients with IPAH. However, patients with PAH associated with Eisenmenger syndrome are an exception because they have a better prognosis than patients with IPAH [69-71].

Patients with severe PAH or right heart failure die sooner, usually within one year without treatment. As an example, patients with IPAH and a mean right atrial pressure ≥20 mmHg have a median survival of approximately one month [71].

Factors that may indicate a poor prognosis include age at presentation greater than 45 years, World Health Organization (WHO) functional class III or IV, failure to improve to a lower WHO functional class during treatment, pericardial effusion, large right atrial size, elevated right atrial pressure, septal shift during diastole, decreased pulmonary arterial capacitance (ie, the stroke volume divided by the pulmonary arterial pulse

pressure), increased N-terminal brain natriuretic peptide level, and perhaps hypocapnia[72-78].

Patients with PAH who experience cardiac arrest rarely survive. In a retrospective study of more than 3000 patients with PAH who required cardiopulmonary resuscitation (CPR), only 6 percent survived for 90 days [79].

PHT IN CRF

Though PHT is a common finding in patients with ESRD, very few studies are available on the association between PHT and ESRD. All the studies show around 30-40% prevalence of PHT in patients with ESRD and more prevalence of PHT among those on HD than those on conservative management.

Studies have been done to find the causative factors of PHT in ESRD. Hormonal and metabolic derangement associated with ESRD might lead to pulmonary arterial vasoconstriction and an increase of the pulmonary vascular resistance [4].

Pulmonary artery pressure (PAP) may be further increased by high cardiac output resulting from the arteriovenous access itself and also worsened by commonly occurring anemia and fluid overload [8]. Subclinical

left ventricular dysfunction also occurs in patients with ESRD, and is evidenced as abnormal myocardial diastolic rather than systolic dysfunction [9].

Local vascular tone and function of pulmonary vessels are regulated by the balance between vasodilators, such as nitric oxide, and vasoconstrictors, such as thromboxane [10]. Patients with CRF show an endothelial dysfunction related to defective nitric oxide activity, which is not corrected by hemodialysis (HD) [11]. Increased brain natriuretic hormone is associated with age, left ventricular hypertrophy, renal failure, and PHT. N-terminal pro-brain natriuretic peptide (NT-proBNP) is a byproduct of brain natriuretic peptide (BNP) that has been shown to be of prognostic value in PHT [15].

METHODOLOGY

METHODOLOGY

Study Method

The study was conducted on patients attending the in-patient/out-patient department of nephrology in PSG hospital. All patients with a diagnosis of ESRD where taken up for the study after the application of the inclusion and exclusion criteria and after obtaining consent. These patients were divided into two groups – those who receive dialysis and those on conservative management.

The biochemical data collected were the average of the last six readings.ECG, CXR and echocardiography to assess PHT were done to those patients who were selected to be included in the study.

Study Place

The study was conducted in PSG Hospitals, Coimbatore.

Study Population

Patients diagnosed with end stage renal disease presenting to PSG hospitals during a time period of 6 months were included in the study after the application of inclusion and exclusion criteria.

Study Period

The study was conducted during the time period of April 2010 to October 2010. All patients with a diagnosis of ESRD attending the Nephrology department who gave consent to be included in the study were included during this time period. Total of 73 patients were studied.

Inclusion Criteria

ESRD patients on HD or conservative management were selected. ESRD due to all etiologies and patients of all age groups were selected.

Exclusion Criteria

COPD

Parenchymal Lung Disease

Chest Wall Disease

Previous history of PHT

Previous pulmonary embolism

Smoker (>5 pack years)

Collagen Vascular Disease

LV EF <50%

Significant mitral/aortic valve disease

HD patients were being treated with standard bicarbonate dialysis for 4 hours, 3 times a week. Subjects gave their informedconsent and the study protocol was approved by the institute'sCommittee on Human Research.

ESRD: Established kidney failure (GFR <15 mL/min/1.73 m^2, or permanent renal replacement therapy (RRT)

Thorough medical history and clinical examination*:* A completehistory was recorded with special emphasis to detect any clinical condition that predisposes to PHT, comorbidities, andhistory of renal disease (etiology of renal failure, age at onset, durationof HD therapy, and access location, brachial or radial).

Chest radiography and a standard 12-lead ECG*:* ECG findingssuggestive of PHT were as follows:

(1) right axis deviation

(2) a tall R-wave and small S-wave with a R/S ratio >1 in lead V1

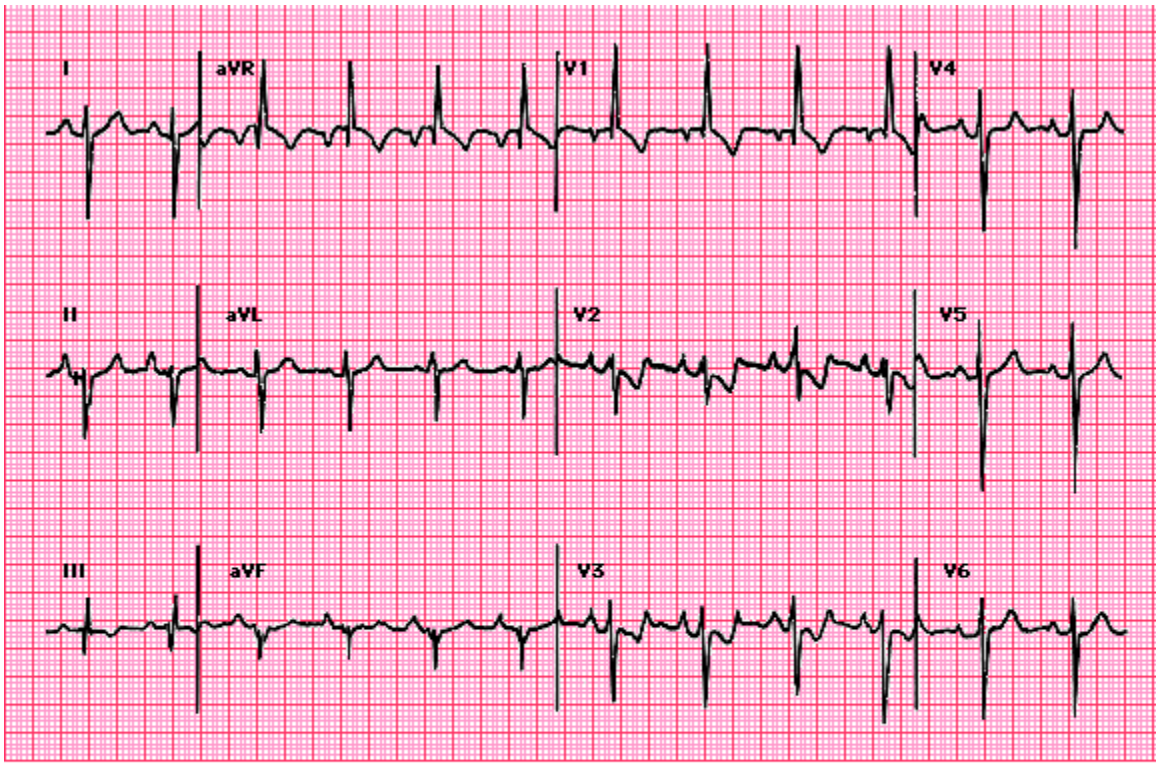
(3) qR complex in lead V1

(4) rSR'pattern in lead V1

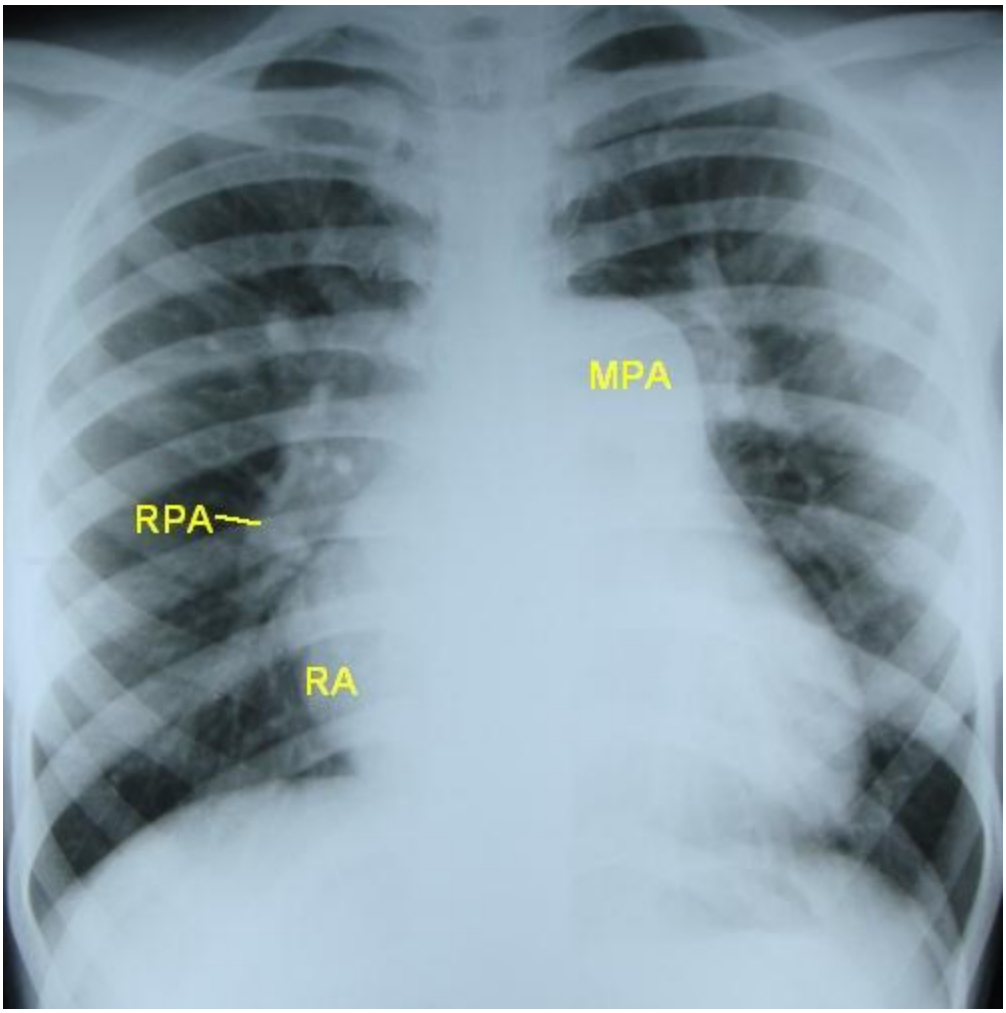
(5) largeS-wave and small R-wave with R/S ratio <1 in lead V5 or V6

(6) S1, S2, S3 pattern.

ST-T segment wave depression and inversion are often present in the right precordial leads. Right atrial enlargementis manifested as a tall P-wave (2.5 mm) in leads II, III,and AVF and frontal P-axis of 75°.



Right ventricular hypertrophy Right ventricular hypertrophy due, in this case, to primary pulmonary hypertension. The characteristic features include marked right axis deviation (+210° which is equal to −150°), tall R wave in V1 (as part of a qR complex), delayed precordial transition zone with prominent S waves in leads V5 and V6, inverted T waves and ST depression in V1 to V3 consistent with right ventricular "strain", and peaked P waves in lead II consistent with concomitant right atrial enlargement. Courtesy of Ary Goldberger, MD.

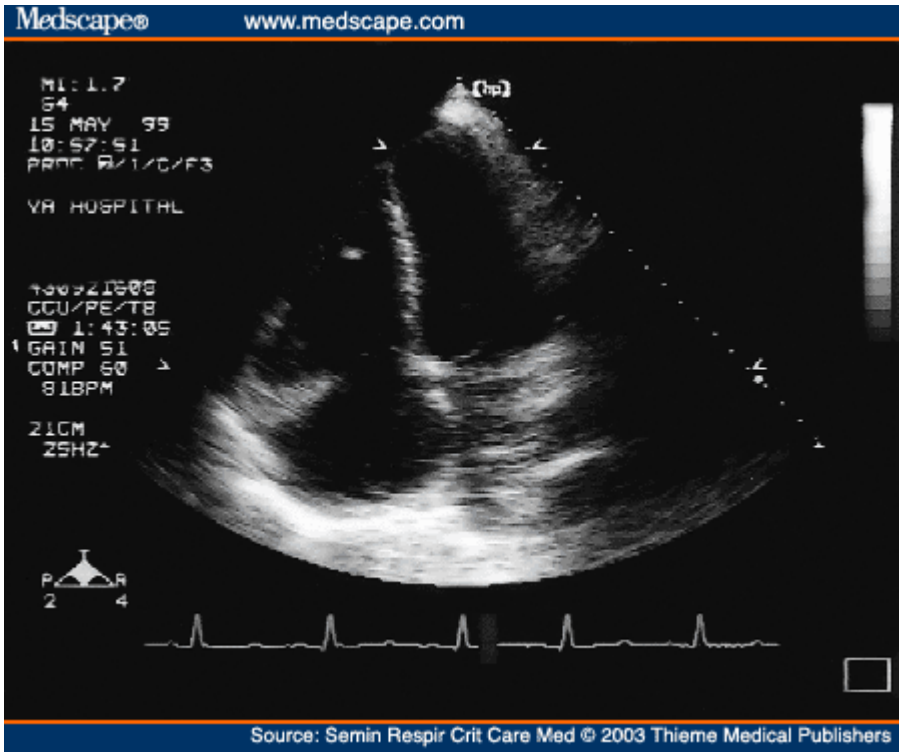


The main pulmonary artery and branch pulmonary arteries are more prominent and so is the right atrial contour.The striking feature in this chest X-ray is the remarkably prominent main pulmonary artery segment (MPA).

Laboratory investigations*:*The mean values from the 6 monthspreceding the echo study were presented for urea, creatinine,hemoglobin, calcium, phosphorus and alkaline phosphatase.

Doppler echocardiography*:* Two-dimensional and M-modeechocardiography were performed in all patients within 4 hours

followingdialysis when the patients were at optimal dry weight accordingto hydration status, blood pressure and weight. Cardiac dimensions were measured according to theguidelines of the American Society of Echocardiography. Systolic right ventricular (or pulmonary artery) pressure wascalculated using the modified Bernoulli equation: PAP = 4 X (tricuspidsystolic jet) ^{2} + 10 mm Hg (estimated right atrial pressure). Stroke volume estimated from the left ventricular outflowtract velocity time integral X diameter cardiac output was calculatedby multiplying the stroke volume by theheart rate. PHT was defined as a systolic PAP > 35 mm Hg



Echocardiogram demonstrating dilatation of the right atrium and ventricles on an apical four-chamber view. The left ventricle chamber dimensions are normal.

RESULTS

RESULTS

Etiology of ESRD

Etiology	Group 1	Group 2
DM	8(21.6%)	11(30.55%)
SHT	8(21.6%)	8(22.22%)
Glomerulonephritis	5(13.5%)	5(13.88%)
Intestitial Nephritis	3(8.10%)	3(8.33%)
Unknown	5(13.5%)	4(11.11%)
Drug Induced	2(5.40%)	3(8.33%)
Obstructive Uropathy	2(5.40%)	0
Chronic Pyelonephritis	1(2.70%)	0
SLE	2(5.40%)	2(5.55%)
PAN	1(2.70%)	0

Group 1: Patients on HD

Group 2: Patients on conservative management

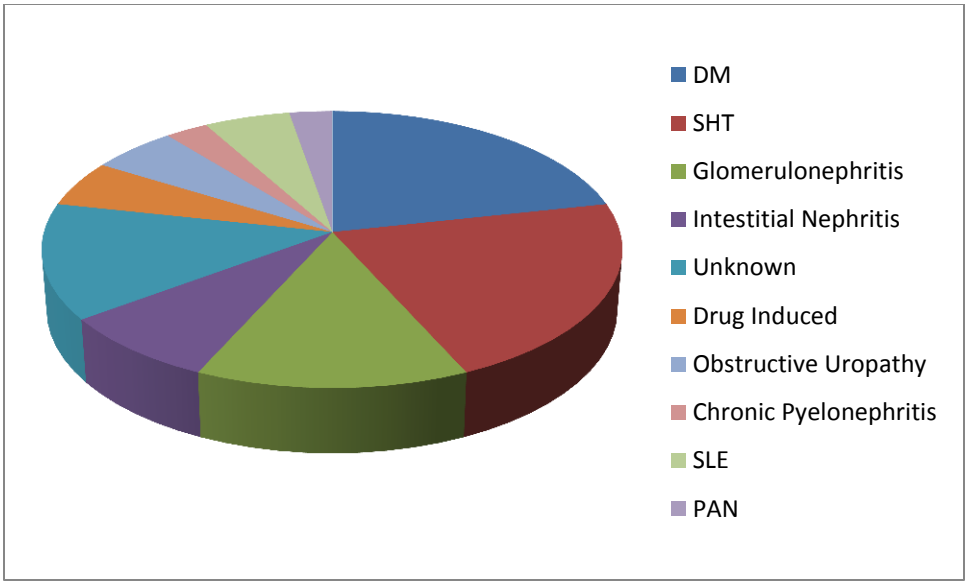


Figure 1: Etiology of ESRD of group 1

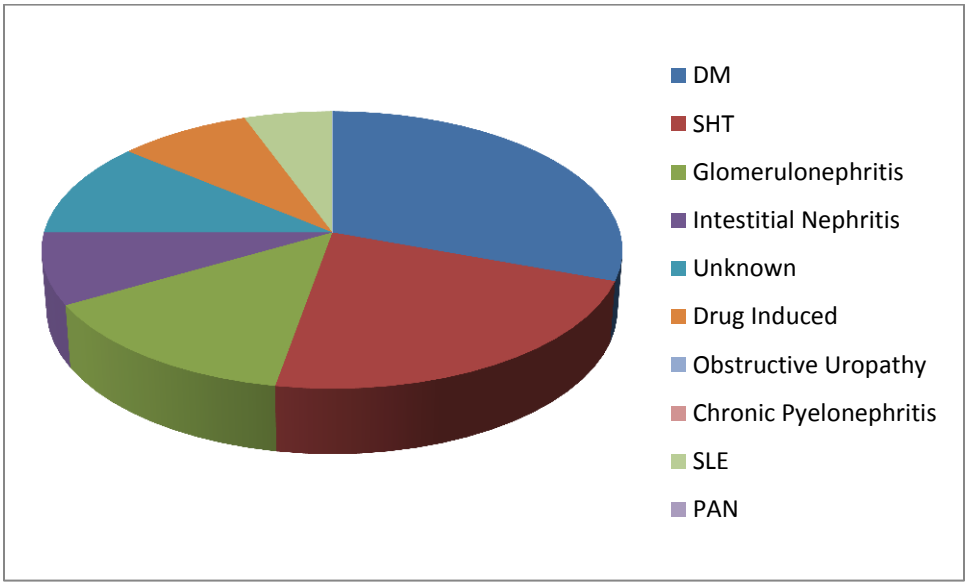


Figure 2: Etiology of ESRD of group 2

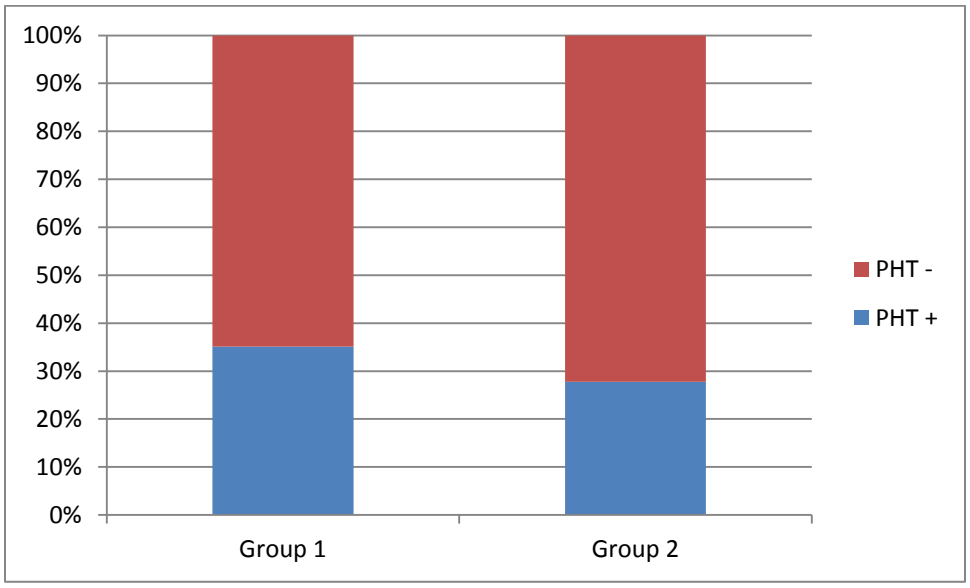
Demographic and dialysis data (Average)

Variable		Group 1	Group 2
Age		55.94	55.75
Gender			
	Males	20	22
	Females	17	14
Duration of dialysis		18.91	-
AV access location			
	Radial	21	22
	Brachial	16	14
ECG			
	Positive	7	3
	Negative	30	33

Group 1: Patients on HD

Group 2: Patients on conservative management

Percentage of PHT positive patients among the two groups



Group 1: 35% have PHT

Group 2: 28% have PHT

Biochemical data of groups 1 and 2 (Average)

Variable	Group 1	Group 2	p value
Urea	153.24	83.05	<0.01
Creatinine	8.79	3.99	<0.01
Hb	9.79	10.48	<0.01
Calcium	8.54	9.26	<0.01
Phosphorus	5.27	4.80	<0.01
Alk Phosphatase	334.43	135.30	<0.01

Group 1: Patients on HD

Group 2: Patients on conservative management

Data of pulmonary hypertensive and non-hypertensive groups

Variables		PAH +	PAH -	p value
Age		61.30	53.04	<0.01
Sex	Male	14	27	
	Female	9	22	
Location of AVF	Brachial	9(39.13%)	20(40.81%)	
	Radial	14(60.87%)	29(59.19%)	
Urea		159.95	100.61	<0.01
Creatinine		7.68	5.90	<0.01
Hb		9.84	10.27	0.11
Calcium		8.66	9.03	0.08
Phosphorus		5.19	4.98	0.18
Alk Phosphatase		314.52	201.63	<0.01
ECG	Positive	10	0	
	Negative	13	49	

DISCUSSION

DISCUSSION

PHT in HD patients and in patients with ESRD in the pre-dialysis stage were studied and elevated pulmonary artery systolic pressure (>35 mm Hg) was found in 35% in group 1 and 28% in group 2. The total incidence was 31.5% among ESRD patients.

Results show that PHT is more common among those on hemodialysis than those who are on conservative management. The causeof a higher PAP in group 1 may be related to the process of HD or the hemodynamic changes caused by AVF.The process of HD itself may be a contributing factor for elevated PAP, but the exact cause is not known and vasoconstrictors such asendothelin may be involved. Microbubble emboli are another cause. In addition, HD causes recurrent episodes of hypoxemia due to partial blockage of the pulmonary capillary bed by white cells or silicone microemboli. Recurrent hypoxemia is associated with elevation of PAP.

Other studies have found a significant difference between groups 1 and 2 with regard to Thromboxane B2 and pro-BNP. The increase of TXB 2 in the HD group may be related to the process of HD which induces a

detectable extracorporeal increaseof TXB 2 through blood membrane interaction causingdegranulation of neutrophils. NT-proBNP is possibly largely eliminated by glomerular filtration only, so its level is elevated in patients with renal failure.

In this study, patients with PHT have a significantly higher age than those without PHT. They also have higher levels of serum urea and serum creatinine.The effect of uremic toxin on PAP had been postulated as an etiological factor in HD-associated PHT through endothelial dysfunction that has been described in PHT and uremia, which diminishes the vasodilatation response to the arteriovenous access-induced elevated cardiac output.

Patients with PHT show no significant difference from those without regarding hemoglobin, serum calcium and serum phosphorus. Although anemia is associated with a compensatory increased cardiac output and is expected to be one of the causes of increased cardiac output, it seems that its contribution is minimal in patients with PHT. This study also shows a significantly elevated alkaline phosphatase level in patients with PHT the significance of which is not yet known.

Limitations:

AV fistula flow velocities were not studied since compression of the AVF can lead to closure of the fistula.

Thromboxane B2, NT Pro-BNP and Parathormone levels were not studied due to financial reasons.

CONCLUSION

CONCLUSION

- This study shows that PHT is very common in ESRD patients.
    a. 31.5% of total patients (73) with ESRD had PHT
    b. 35% of 37 patients on HD had PHT
    c. 28% of 36 patients on conservative management had PHT

- Also, PHT is much more common in ESRD patients receiving HD than those on conservative management.

- Since pulmonary arterial hypertension usually presents at a very late stage, early diagnosis is a key to proper management and a better outcome.

- Estimation and follow-up of PAP using doppler echocardiography may be indicated in all patients with ESRD undergoing HD via an arteriovenous access.

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APPENDIX

PROFORMA

Pulmonary Hypertension in ESRD

Name : IP/OP NO. :
Age/Sex :

Cause of Renal Failure: Duration of AVF:
Duration of ESRD: Location of AVF:

History of Lung Disease

COPD: Parenchymal Lung Disease:
Previous history of PHT: Chest Wall Disease:
Previous pulmonary embolism: Collagen Vascular Disease:
Smoker (>5 pack years): Significant mitral/aortic valve disease:
LV EF <50%:

General Examination

CVS:

BP:

RS:

PR:

P/A:

ECG:

CXR:

Biochemical Data

	1	2	3	4	5	6	Average
Urea							
Creatinine							
Hemoglobin							
Calcium							
Phosphorus							
Alk. Phosphotase							

Echocardiogram

Presence of valvular heart disease:

LVEF:

PAP: